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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,870	03/21/2001	Philip A. Cole	01107.00108	8634
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BANNER & WITCOFF				STEADMAN, DAVID J
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WASHINGTON, DC 20001				
ART UNIT				PAPER NUMBER
1652				

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

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Amendment due

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Office Action Summary	Application No.	Applicant(s)
	09/811,870	COLE ET AL.
	Examiner David J Steadman	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 29 September 2004.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-15, 58, 60, 63, 66, 67 and 69-76 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-15, 58, 60, 63, 66-67, and 69-76 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____.
 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____.

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DETAILED ACTION

Status of the Application

- [1] Claims 1-15, 58, 60, 63, 66-67, and 69-76 are pending in the application.
- [2] Applicants' amendment to the claims, filed September 29, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
- [3] Receipt of a Declaration by inventor Cole, filed September 29, 2004, is acknowledged.
- [4] Applicants' arguments filed on September 29, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [5] The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

- [6] Claims 1, 4-15, 58, 60, 63, 66-67, and 69-76 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
- [a] Claims 1 (claims 4-14 and 58 dependent therefrom) and 60 (claims 63, 66-67, and 69-76 dependent therefrom) are indefinite in the recitation of "nucleotide analog" as it is unclear as to the structural/functional characteristics a compound must possess in

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order to be included within the scope of recited nucleotide analogs. For example, must a compound merely comprise a triphosphate to be included within the scope of recited "nucleotide analogs?" Or are additional structural features required for inclusion? It is suggested that applicants clarify the meaning of the term.

[b] Claims 8-9 are confusing in that it is unclear as to how the recited nucleotide or analog thereof is to comprise a triphosphate and simultaneously have the phosphate groups replaced by alkyl groups. It is suggested that applicants clarify the meaning of the claims.

[c] Claim 15 is unclear in the recitation of "Compound 2." While it is noted that a compound labeled only as "2" is disclosed in the specification (see Figure 1, part a), the examiner can find no compound that is specifically labeled "Compound 2." Clarification is requested. In the interest of advancing prosecution, the compound labeled as "2" in Figure 1, part a has been interpreted as being "Compound 2."

[d] Claims 69-71 and 74 are indefinite in the recitation of "natural substrate" as it is unclear as to the scope of peptide moieties that are intended to be encompassed by the term "natural substrates" and those peptides that are considered to be unnatural substrates. It is suggested that applicants clarify the meaning of the term.

[7] The rejection of claims 1-14, 58, 60, 63, 66-67, 69-71, and 74-76 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of (as amended) "the tether is greater than or equal to 4.9 Å measured from a gamma phosphorous of the nucleotide or nucleotide analog moiety to a proton donor" is maintained for the reasons

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of record as set forth at item [7] part [a] of the Office action mailed April 29, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue the specification clearly teaches a skilled artisan how to calculate the recited distance. Specifically, applicants argue the specification teaches (p. 4) the use of Cambridge Soft's Chem3D software to calculate the recited distance assuming an extended conformation of the acetyl linker, meaning that the structure is relaxed to allow the atoms to be as far apart as possible within a covalent structure, assuming standard atomic radii for the covalent bonds and standard bond angles. Applicants' argument is not found persuasive.

The examiner acknowledges the disclosure that the "[d]istance between the anilino nitrogen and the gamma-phosphorous was calculated using Chem3D assuming an extended conformation of the acetyl linker" (page 4, paragraph [17]). However, there is no evidence of record that would indicate that the measurement of the recited distance is limited to being calculated using Cambridge Soft's Chem3D software assuming an extended conformation of the acetyl linker. MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation in light of the specification without importing limitations from the specification into the claims. As such, the measurement of the tether of the bisubstrate inhibitor can be made by any method using an extended or non-extended conformation of the molecule. As such, it is unclear as to the scope of the tethers that are to be included or excluded from the claimed bisubstrate inhibitors and consequently, it is unclear as to the scope of bisubstrate

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inhibitors encompassed by the claims. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The written description rejection of claims 1-14, 58, 60, 63, 66-67, and 69-76 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth at item [8] of the Office action mailed November 17, 2003 and item [9] of the Office action mailed April 29, 2004 and for the reasons stated below.

RESPONSE TO ARGUMENTS: Applicants argue the inhibitors of claims 1 and 60 recite identifying characteristics of the genus of inhibitors. Specifically, applicants argue the claims recite: 1) a nucleotide or analog thereof comprising a triphosphate and are further limited by claims 2-3 and 8-9; 2) a peptide moiety that comprises a specific amino acid that is further limited by claims 4-7, 10-14, and 69-71; 3) identifying characteristics of the relationship between the nucleotide or analog thereof and the tether; and 4) identifying characteristics of the peptide moiety-tether linkage. Addressing the genus of IRK inhibitors, applicants argue the previously identified 19 natural substrate peptides of IRK, and using these peptides along with the ten nucleotides and analogs thereof and a simple 2-carbon tether taught in the specification, at least 190 inhibitors of IRK can be constructed as representative species. Addressing the genus of protein kinase inhibitors, applicants argue the previously identified 82 natural substrate peptides of protein kinases, and using these peptides along with the ten nucleotides and analogs thereof and a simple 2-carbon tether taught in the specification, at least 820

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inhibitors can be constructed as representative species. Applicants further argue that the Cole Declaration presents five additional species made according to the specification. Applicants' argument is not found persuasive.

Regarding the Cole Declaration, applicants are reminded that the five species as disclosed in the Cole Declaration were not available to a skilled artisan at the time of the invention as these species were neither disclosed in the instant specification nor the prior art. Regarding the alleged 190 IRK inhibitors or 820 protein kinase inhibitors that "have been described in the specification," it is noted that the *specification* actually discloses *only a single* IRK bisubstrate inhibitor and *only two* representative examples of protein kinase inhibitors.

Regarding the merits of applicants' argument, the examiner maintains the position that the single disclosed representative species of IRK bisubstrate inhibitor and the two disclosed representative species of protein kinase inhibitors, even in view of the teachings of the prior art, fail to describe the entire genus of claimed inhibitors.

Addressing the nucleotide or analog thereof, it is noted that the nucleotide analog is not limited to those disclosed in the specification and, if broadly interpreted in accordance with MPEP 2111, can have essentially any structure that comprises a triphosphate.

Addressing the peptide moiety, there is no disclosed structure-function relationship between the structure of the peptide moiety and its "function" as being a substrate for any IRK or any protein kinase. Further, it should be noted that, while the peptide is limited to comprising one specific amino acid, the peptide is unlimited with respect to its remaining structural features and is unlimited with respect to the length and size of the

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peptide. Addressing the tether, the structure of the tether is essentially undefined, being limited only to having a measurement greater than or equal to 4.9 Angstroms as recited in the broadest claims. In view of the lack of defining structural characteristics for the claimed inhibitors, the genus of inhibitors encompasses species that are widely variant in structure, which, it is noted, is undisputed by applicants. It should be noted that the wide variability in the genus of inhibitors is evidenced by applicants' disclosure of alleged IRK and protein kinase peptide substrates (see Attachment 3 of the response filed September 29, 2004), which have widely varying structures. Also, regarding claims 58 and 67, the specification fails to provide an adequate description of all IRKs and protein kinases that bind to the claimed inhibitors – such IRKs and protein kinases being an essential or critical feature of the claimed invention thus requiring adequate written description. Further, regarding claims 69-71 and 74, it is noted that the specification fails to disclose those characteristics of the genus of peptide moieties that distinguish the subgenus of protein kinase "natural substrate" peptides from the larger genus of protein kinase substrate peptides. In this case, the representative species fail to describe all members of the genus. At least for the reasons of record and the reasons stated above, the specification – even in view of the prior art – fails to describe all members of the claimed genus of bisubstrate inhibitors.

[9] Claims 1-14, 58, 60, 63, 66-67, and 69-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds 2 and 4, does not reasonably provide enablement for all bisubstrate inhibitors of insulin receptor kinase or any protein kinase as encompassed by the claims. The specification does not

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enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is noted that the examiner inadvertently omitted claims 69-76 from the scope of enablement rejection in the Office action mailed April 29, 2004. The reasoning for rejecting claims 1-14, 58, 60, 63, and 66-67 as set forth at item [10] of the Office action mailed April 29, 2004 also applies to claims 69-76.

RESPONSE TO ARGUMENTS: Applicants argue the breadth of the claims has been limited by further defining the structural features of the recited nucleotide or analog thereof, peptide moiety, and tether. Applicants argue the state of the art at the time of the invention was advanced with regard to nucleotides and analogs thereof and natural and non-natural IRK and protein kinase substrates. Applicants argue the skill in the art was high at the time of the invention as the skilled artisan would have knowledge of natural and non-natural peptide substrates and of nucleotides and analogs thereof and one could easily link the peptide and nucleotide or analog thereof in accordance with the linking requirements. Applicants argue the level of predictability at the time of the invention was high in view of the prior art and in view of the specific linking requirements and that the Cole declaration presents five additional inhibitors. Applicants argue the specification provides guidance regarding the composition, length, and determination of length of the tether. Applicants argue the quantity of experimentation is not undue as all component parts of the claimed inhibitors were known and one of skill merely need assemble the parts. Applicants' argument is not found persuasive.

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In response to applicants' argument that the breadth of the claims has been limited by further defining the structural features of the recited nucleotide or analog thereof, peptide moiety, and tether, it is noted that, aside from the requirement that the nucleotide analog comprise a triphosphate and the single required amino acid of the peptide moiety of claims 1 and 60, the structures of the components are essentially unlimited. The nucleotide analog can be essentially any structure that has a triphosphate, the peptide moiety can be any polypeptide amino acid sequence of any length and composition that comprises the required single amino acid, and the tether can be any structure (not limited to being composed of O, C, and H), with an unlimited length. Moreover, with regard to claims 58 and 67, the claims encompass a complex between an inhibitor as broadly encompassed by the claims and any IRK or protein kinase, including mutants and variants of known IRKs or protein kinases.

In response to applicants' argument that the state of the art at the time of the invention was advanced and the skill in the art was high at the time of the invention, it should be noted that, while a skilled artisan may have had knowledge regarding those nucleotide analogs and peptide moieties that were known in the art, the claims are not limited to art-recognized nucleotide analogs and peptide moieties nor is the tether limited to those tethers that are disclosed in the specification. As stated above, the nucleotide analog can be essentially any structure that has a triphosphate, the peptide moiety can be any polypeptide of any length and any amino acid composition that comprises the required single amino acid, and the tether can be any structure of any composition (not limited to being composed of O, C, and H), with an unlimited length.

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In response to applicants' argument that the level of predictability at the time of the invention was high, it is noted that, regarding the nucleotide analog and peptide moiety, the level of predictability at the time of the invention may have been high for linking those nucleotide analogs as specifically disclosed in the specification with art-recognized peptide moieties using a linker as specifically disclosed in the specification with an expectation that the inhibitor would have the ability to inhibit the cognate IRK or protein kinase. However, the claims are not so limited. In view of the broad scope of individual components of the claimed inhibitors as described above, one would not have had a reasonable expectation of joining essentially any structure that has a triphosphate with a peptide moiety that can be any polypeptide structure that comprises the required single amino acid with a tether that can have any structure of any composition (not limited to being composed of O, C, and H), with an unlimited length with an expectation of inhibiting a desired IRK or protein kinase. While the evidence of the Cole Declaration has been considered, it is noted that the inhibitors of the Cole Declaration appear to employ the same nucleotide and tether as disclosed in compound 2 of the specification and it is not clear as to whether the recited peptides were known in the art at the time of the invention. It should also be noted that the peptides denoted as D. and E. in the Cole Declaration do not meet the limitations of the claimed inhibitor as these peptide moieties do not have the required amino acid as recited in the claims. Also, the examiner reiterates the teachings of Parang et al. and Miller et al. (cited in a previous Office action), which provide evidence regarding the unpredictability at the time of the invention.

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In response to applicants' argument that the specification provides guidance regarding the composition, length, and determination of length of the tether, it is noted that the disclosure that the tether can be composed of C, H, or O atoms and should have the linking requirement of greater than 4.9 Angstroms as recited in the claims, one of skill in the art would recognize that this is not sufficient guidance for making the full scope of recited tethers that can have any structure of any composition (not limited to being composed of O, C, and H), with an unlimited length. Further, while the specification teaches that the tether *can* be measured using Chem3D, the claims are not so limited, and as stated above, in view of the indefiniteness of how one is to measure the distance of the tether, this guidance fails to enable the full scope of recited tethers.

In response to applicants' argument that the quantity of experimentation is not undue as all component parts of the claimed inhibitors were known and one of skill merely need assemble the parts, it is noted that, as stated above, while one of skill may have been able to link those nucleotide analogs as specifically disclosed in the specification with art-recognized peptide moieties using a linker as specifically disclosed in the specification with an expectation that the inhibitor would have the ability to inhibit the cognate IRK or protein kinase, the claims are not so limited to those nucleotide analogs or peptide moieties that were known in the art and is not limited to those tethers that are disclosed in the specification. Also, regarding claims 58 and 67, the claims are not so limited to a complex between an inhibitor as broadly encompassed by the claims and an art-recognized IRK or protein kinase. Thus, in view of the broad scope of the

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claims, the lack of guidance and working examples to support the broad scope of the claims, and the level of unpredictability, the amount of experimentation required to make the full scope of the claims would not be considered routine. Consequently, undue experimentation would have been required to make the full scope of claimed inhibitors.

Claim Rejections - 35 USC § 102

[10] In view of applicants' amendment to the claims, the rejection of claims 60, 67, 69-70, and 74 under 35 U.S.C. 102(b) as being anticipated by Ricouart et al. as set forth at item [11] of the Office action mailed April 29, 2004, is withdrawn. The nucleotide analog of the PKA/PKC inhibitor of Ricouart et al. does not comprise a triphosphate and the examiner can find no teaching in the prior art to modify the PKA/PKC inhibitors as taught by Ricouart et al. by adding a triphosphate to the nucleotide analog of the inhibitor such that the triphosphate is linked to the spacer.

Conclusion

[11] Status of the claims:

- Claims 1-15, 58, 60, 63, 66-67, and 69-76 are pending.
- Claims 1-15, 58, 60, 63, 66-67, and 69-76 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Thursday from 7:30 am to 5:00 pm and on alternate Fridays from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. Any inquiry of a general nature or

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relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

 10-25-04

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652